



Europäisches Patentamt

European Patent Office

Office européen des brevets

(19)

(11) Publication number:

0 206 726

A2

(12)

## EUROPEAN PATENT APPLICATION

(21) Application number: 86304643.9

(51) Int. Cl.: A 61 L 27/00

(22) Date of filing: 16.06.86

(30) Priority: 19.06.85 US 746342

(71) Applicant: UNIVERSITY OF FLORIDA, 207 Tigert Hall,  
Gainesville Florida 32611 (US)

(43) Date of publication of application: 30.12.86  
Bulletin 86/52

(72) Inventor: Low, Samuel Bernard, 2435 N.W. 35th Terrace,  
Gainesville Florida 32601 (US)  
Inventor: Fetner, Alan Edward, 6508 N.W. 53rd Terrace,  
Gainesville Florida 32606 (US)  
Inventor: Clark, Arthur Edward, Jr., 2901 N.W. 41st  
Avenue, Gainesville Florida 32605 (US)  
Inventor: Hench, Larry Leroy, 1415 N.W. 94th Street,  
Gainesville Florida 32606 (US)  
Inventor: Wilson-Hench, June, 1415 N.W. 94th Street,  
Gainesville Florida 32606 (US)

(84) Designated Contracting States: AT BE CH DE FR GB IT LI  
LU NL SE

(74) Representative: Hedley, Nicholas James Matthew et al,  
T.Z. Gold & Company 9 Staple Inn, London WC1V 7QH  
(GB)

(54) **Periodontal osseous defect repair.**

(57) The present invention provides a composition for repair of periodontal osseous defects based on particulate bioactive and biocompatible glass. The particulate glass has a particle size in the range of 90 to 710  $\mu\text{m}$ , preferably it is a mixture of

- (1) glass having a particle size of 90 to 355  $\mu\text{m}$ ,
- (2) glass having a particle size of 355 to 500  $\mu\text{m}$ , and
- (3) glass having a particle size of 500 to 710  $\mu\text{m}$ .

The glass composition is as follows:

Component	Weight Percentage
SiO <sub>2</sub>	40-52
CaO	10-50
Na <sub>2</sub> O	10-35
P <sub>2</sub> O <sub>5</sub>	2-8
CaF <sub>2</sub>	0-25
B <sub>2</sub> O <sub>3</sub>	0-10

EP 0 206 726 A2

## PERIODONTAL OSSEOUS DEFECT REPAIR

Background of the InventionField of the Invention

5 The present invention relates to compositions and methods for the repair of periodontal osseous defects.

Prior Art

10 Historically, clinicians have used numerous and varied materials in the attempt to repair periodontal osseous defects. Autogenous grafts have been used with varying degrees of success [Schallhorn, R.G.: Present status of osseous grafting procedures.

15 J. Periodontal 28: 570, 1977; Dragoo, M.R., and Sullivan, H.C.: A clinical and histological evaluation of autogenous iliac bone grafts in humans. Part I, wound healing 2 to 8 months. J Periodontol 44: 599, 1973] but difficulties in obtaining sufficient

20 quantities and the frequent need for a second surgical procedure present obvious disadvantages [Moskow, B.S., Karsh, F., and Stein, S.D.: Histological assessment of autogenous bone--a case report and critical evaluation. J Periodontal 50: 291, 1979.] Allografts

25 [Mellonig, J.T., Bowers, G.M., Bright R.W., and Laurene, J.J.: Clinical evaluation of freeze-dried bone allografts in periodontal osseous defects. J. Periodontal 47: 125, 1976; Sepe, W.W., Bowers, G.M., Lawrence, J.J., Friedlaender, G.E., and Koch, R.W.:

30 Clinical evaluation of freeze-dried bone allografts in periodontal osseous defects. Part II. J Periodontal 49: 9, 1978] have also provided promising results, but limited availability and questions of their immunogenicity still exist [Sanders, J.J., Sepe, W.W., Bowers G.M., Koch, R.W., Williams, J.E., Lekas, J.S.,

Mellonig, J.T., Pelleu, G.B., Gambill, V.: Clinical evaluation of freeze-dried bone allografts in periodontal osseous defects. Part III. Composite freeze-dried bone allografts with or without 5 autogenous bone grafts. J Periodontol 54: 1, 1983.] In order to overcome these problems, recent attention has been directed toward developing suitable alloplastic materials for such repair procedures.

Tricalcium phosphate ceramic  $\text{Ca}_3(\text{PO}_4)_2$   
10 (TCP) and Hydroxylapatite ceramic  
 $(\text{Ca}_1\text{O}(\text{PO}_4)_6(\text{OH})_2)$  (HA) have been widely investigated. These materials are considered biologically inert, producing no inflammatory response when implanted [Jarcho, M., Bolen, C.H., Thomas, M.B.,  
15 et al.: Hydroxylapatite synthesis and characterization in dense polycrystalline form. J Mater Sci 11: 2027, 1976; Moskow, B.S., Lubarr, A.: Histological assessment of human periodontal defect after durapatite ceramic implant. J Periodontol 54: 455,  
20 1983; Froum, S.Sj., Kushner, L., Scopp, I.W., and Stahl, S.S.: Human clinical and histologic responses to durapatite implants in intraosseous lesions--case reports. J Periodontol 53:719, 1982; Baldock, W.T., Hutchens, Jr., L.H., McFall, Jr., W.T., Simpson, D.M.:  
25 An evaluation of tricalcium phosphate implants in human periodontal osseous defects of two patients. J. Periodontol 56:1, 1985] Rabalais, M.L., Yukna, R.A., and Mayer, E.T. [Evaluation of durapatite ceramic as an alloplastic implant in periodontal osseous defects.  
30 I. Initial six month results. J. Periodontol 52: 680, 1981] found, on reentry, greater fill with HA (durapatite) than debridement alone. Others (Nery, E.B., and Lynch, K.L.: Preliminary studies of bioceramic in periodontal osseous defects. J.  
35 Periodontol 49: 523, 1978; Strub, J.R., Gaberthuel,

T.W. and Firestone, A.R.: Comparison of tricalcium phosphate and frozen allogenic bone implants in man. J Periodontol 50: 624, 1979] have found similar bone fill with TCP. However, histologic evaluations have 5 given little evidence of new attachment with either of these materials [Moskow, B.S., Lubarr, A.: Histological assessment of human periodontal defect after durapatite ceramic implant. J Periodontol 54: 455, 1983; Froum, S.Sj., Kushner, L., Scopp, I.W., and 10 Stahl, S.S.: Human clinical and histologic responses to durapatite implants in intraosseous lesions--case reports. J Periodontol 53: 719, 1982; Meffert, R.M., Thomas, J.R., Hamilton, K.M., Brownstein, C.N.: Hydroxylapatite as an alloplastic graft in the 15 treatment of human periodontal osseous defects. J Periodontol 56: 63-74, 1985.]

Bioactive and biocompatible glasses have been developed as bone replacement materials. Studies have shown that these glasses will induce 20 osteogenesis [Hench, L.L., Splinter, R.J., Allen, W.C. et al: Bonding mechanisms at the interface of ceramic prosthetic materials. J Biomed Mater Res 1971; 5: 117-141; Hench, L.L., Paschall, H.A.: Direct chemical bond of bioactive glass-ceramic materials to bone and 25 muscle. J Biomed Mater Res 1973; 7:25-42; Clarke, A.E., Pantano, C.G., and Hench, L.L.: Compositional Analysis of the formation of a bone-implant bond, Symposium on materials for reconstructive surgery, Clemson University, April, 1975; Clarke, A.E., 30 Paschall, H.A., and Hench, L.L.: The influence of surface chemistry on implant interface histology; A theoretical basis for implant materials selection, J Biomed Materials Research, Vol. 10, No. 2, pg. 161-174, March, 1976; Hench, L.L., and Wilson, J.: 35 Surface-Active biomaterials. Science 226, pp. 630-636,

1984; Hench, L.L., and Clarke, A.E.: "Adhesion of  
bone", Biocompatibility of Orthopaedic Implants, Vol.  
II, Editor-David F. Williams, pg. 129-170, CRC Press,  
Inc., Boca Raton, Florida, 1982} when implanted in  
5 bone. The interfacial bond between the implant and  
bone has been demonstrated to be extremely strong  
(Piotrowski, G., Hench, L.L., Allen, W.C., and Miller  
G.J.: Mechanical Studies of the Bone Bioglass  
Interfacial Bond. J. Biomed Mater Res. Symp, 9: 47-61,  
10 1975.]

The so-called 45s5 or S, bioactive glass  
formulation has been widely tested. The substitution  
of CaF<sub>2</sub> (calcium fluoride) for a variable percentage  
of the CaO (calcium oxide) yields the F formulations.  
15 Toxicology evaluation of the glasses [summarized by  
Wilson, J., Schoen, F.J., Pigott, G.H., et al:  
Toxicology and biocompatibility of bioglasses. J  
Biomed Mater Res 1981; 805-817] has shown no toxic  
effects in bone or soft tissue in numerous in vitro  
20 and in vivo models.

The bonding of the glass to bone begins with  
exposure of the glass to aqueous solutions. Na<sup>+</sup> in  
the glass exchanges with H<sup>+</sup> from the body fluids  
causing the pH to increase. Ca and P migrate from the  
25 glass forming a Ca-P rich surface layer. The  
thickness of the Ca-P rich zone remains at 30-40  
microns with an underlying silica rich zone slowly  
increasing in dimension as the Na<sup>+</sup> in the glass  
continues to exchange with the H<sup>+</sup> of the solution.

30 Initially the Ca-P rich layer is amorphous,  
but within 7-10 days it crystallizes into an  
hydroxyapatite-like material. Collagen, either in  
vitro or in vivo, becomes structurally integrated in  
the apatite agglomerates. A zone forms between the  
35 collagen and surface active glass in vivo that is

- 5 -

80-100 nm thick. Osteoblasts in the implant area provide (1) collagen and ground substance, and (2) matrix vesicles for primary mineralization [Gross, U.M., Strunz, V.: Clin. App. Biomaterials, EDS.

5 Albrehtsson and Brane Mark, J. Wiley, pp. 237, 1982.] As maturation continues, evenly distributed osteocytes can be observed.

The behavior of the bioactive glasses as solid implants in a dental application was examined by 10 Stanley, H., Hench, L.L., Going, R., Bennett, C., Chellemi, S.J., King, C., Ingersoll, N., Etheridge, E., and Kreutziger, K. ["The implantation of natural tooth from bioglasses in baboons," Oral Surg. Oral Med. Oral Path., 42, (3), 339-356, 1976.] Replicate 15 tooth forms of glass were fabricated and implanted into extracted incisor sockets of adult baboons. Distinct histopathologic features were associated with the specific formulation used. After six months, the F glass formulation induced ankylosis while another 20 glass formulation induced a fibrous capsule. In the two successful S implants, ankylosis was induced in one with the other producing an apparently normal periodontal ligament. A two year study [Stanley, H.R., Hench, L.L. Bennett, Jr., C.G. Chellemi, S.J. 25 King, C.J. Going, R.E., Ingersoll, N.L., Ethridge, E.C., Kreutziger, K.L., Loeb, L., Clark, A.E.: "The implantation of Natural Tooth From Bioglass in Baboons-Long Term Results," The International Jour of Oral Implantology, pg. 26-36, Vol. 2:2, 1981] 30 consistently found ankylosis of both the F and S formulations.

It is an object of the present invention to provide bioactive and biocompatible glass compositions specifically suitable for the repair of periodontal 35 osseous defects.

Summary of the Invention

The present invention provides a composition suitable for the repair of periodontal osseous defects comprising particulate bioactive and biocompatible glass optionally and preferably adversed with a liquid in an amount sufficient to wet the particles of glass, the particulate glass having a particle size in the range of from about 90 to about 710 $\mu\text{m}$  and the following weight percentage composition:

10

	<u>Component</u>	<u>Weight Percentage</u>
	SiO <sub>2</sub>	40-52
	CaO	10-50
15	Na <sub>2</sub> O	10-35
	P <sub>2</sub> O <sub>5</sub>	2-8
	CaF <sub>2</sub>	0-25
	B <sub>2</sub> O <sub>3</sub>	0-10

20

The invention also provides a method of repairing a periodontal osseous defect comprising applying the above composition to the defect and allowing the composition to harden and bond to surrounding tissue.

25

Detailed Description of the Invention

Presently available synthetic materials for use in the repair of periodontal defects have particle sizes in the range of 300 to 500 $\mu\text{m}$  (Zaner and Yukna J. 30 Periodontol, Vol. 55(7) Page 406 (1984). Autogeneous bone samples have a size ranging from 210 x 105 $\mu\text{m}$  for autogeneous bone blend to 1559 x 783 $\mu\text{m}$  for autogeneous hand chisel bone samples.

In-vitro experiments consisting of the 35 mixing of equal volumes of human blood with equal

volumes of presently used synthetic materials showed that the mixtures were not cohesive. The tricalcium phosphate (TCP) material (Synthograft) was especially noncohesive and tended to float on top of the blood 5 when the mixing action stopped. This is due to the microporous nature of the particles of Synthograft.

Manipulation of the hydroxyapatite (HA) and tricalcium phosphate (Synthograft) powders with a flat instrument such as a spatula or orban knife was 10 exceedingly difficult even after mixing with blood. Manipulation of the HA and TCP powders mixed with sterile water was not improved. In each of these instances it was discovered that only a few granules 15 of the powders remained on the instrument as they were moved from the mixing dish to a simulated periodontal defect. Efforts to pack the HA and TCP powders, either dry or mixed with blood or water into a simulated periodontal defect did not result in a cohesive, space-filling mass. Instead the particles 20 could be easily removed by tilting or slight irrigation. See Table 1.

In contrast to the above observations of the noncohesiveness of presently used synthetic periodontal grafting materials, it was an unexpected 25 discovery that bioactive glass powders of the above compositions and of a specific range of sizes, specific surface areas, specific pore distributions, and specific surface chemistry would form a cohesive mass when mixed with blood.

30 When quantities of blood, ranging from equal volume to one-third equal volume to glass powders, but of sufficient volume to wet thoroughly the glass powder, were mixed for a few seconds to one-half minute with 45S5 and 45S5F glass powders it was 35 discovered that the particles stuck together and

quickly formed a putty-like consistency. The resulting cohesive mixture could be easily picked up by an instrument, both flat and pointed, and passed from the mixing vessel to a simulated implantation site very easily. The cohesive mass of glass powder and blood stuck to the instrument with sufficient cohesion that the mass could be pressed into a simulated site without loss of particles. The resulting cohesive mass once placed in the site remained in place upon tilting or irrigation.

It was further noted that specific size ranges of glass powders were substantially more cohesive than others. The glass powder comprised of 90-355 $\mu\text{m}$  particles easily formed a cohesive mass and was easily manipulated. The larger powder comprised of 500-710 $\mu\text{m}$  particles was less effective in forming a cohesive mass and being manipulated. This behavior was attributed to the smaller surface area of the 500-710 $\mu\text{m}$  powder. However, even the 500-710 $\mu\text{m}$  glass powder was still markedly superior in cohesion and manipulation to HA or TCP dry powders. Addition of 90-355 $\mu\text{m}$  particles to the previously mixed 500-710 $\mu\text{m}$  powder-blood mixture improved both cohesiveness and workability. This suggested that a larger particle size range might produce a more clinically desirable mixture. To test this hypothesis a mixture of equal weight by thirds of 90-355 $\mu\text{m}$  glass particles, 355-500 $\mu\text{m}$  glass particles, and 500-710 $\mu\text{m}$  glass particles (total size range 90-710 $\mu\text{m}$ ) was mixed with blood. The resulting mixture formed an even more cohesive and dense mass with the most superior performance in handling and manipulation.

Table 1

## Behavior of Synthetic Periodontal Packing Materials

Materials	Particle Size (μm)	Ease of Manipulation	Cohesiveness with blood	Appearance in Periodontal Defect
Synthograft (tricalcium phosphate)	250-500	very poor, fell off instrument	none	washed away from site with bleeding
Augmen (porous tri-calcium phosphate)	700-1000	very poor, fell off instrument	none	washed away from site with bleeding
Periograft (hydroxyapatite)	700-1000	poor, tendency to fall off instrument	none	tended to wash from site with bleeding
Alveograft (hydroxyapatite)	700-1000	poor, tendency to fall off instrument	none	tended to wash from site with bleeding
Glass 45S5 or 45S5F	500-710	good remained on instrument	good	moderately, densely packing of particles filling defect
Glass 45S5 or 45S5F	90-355	very good easy to handle & transport	very good, easily packed	very good, dense packing, resistant to irrigation
Glass 45S5 or 45S5F	90-710	excellent superb adh- esion to instrument, superb ease of transport	excellent superior packing	very dense packing in site, translucent, appears in site as if bone resistant to irrigation and suction

- 10 -

The invention is illustrated by the following non-limiting example.

Example

Six adult Patas monkeys (Erythrocebus patas) (five 5 females and one male) were used in the study. The Patas monkey is similar in size and dentition to the Rhesus monkey (Macaca mulatta). All animals had moderate gingivitis associated with heavy supragingival plaque and calculus accumulations.

10 Using Ketamine Hydrochloride (100 mg/ml; 10 mg/kg body weight) the animals received a twice weekly oral hygiene regimen consisting of toothbrushing and 2% chlorhexidine gluconate rinses. The regimen was similar to the one established by Caton, J.G.:

15 Establishing and maintaining clinically healthy gingivae in rhesus monkeys. J Clin Periodontol 6: 260, 1979. The first two cleanings required mechanical instrumentation with ultrasonics and hand instrumentation for removal of calcified deposits.

20 The reduction in clinical inflammation was sustained by continuation of the regimen throughout the study.

Bioactive glasses (Table 2) were prepared by placing the premixed components into a covered platinum crucible, melting at 1350°C and pouring the 25 contents into a container of water. The resultant frit was washed with acetone, ground with a mortar and pestle and sized with a series of calibrated sieves. Three different particle size ranges were obtained for each of the two formulations (Table 3).

30

Table 2 Implant Composition (Weight Per Cent)

	SiO <sub>2</sub>	CaO	CaF <sub>2</sub>	Na <sub>2</sub> O	P <sub>2</sub> O <sub>5</sub>
S (45S5)	45	24.5		24.5	6
F (45S5.4F)	43	14	13	24	6

Table 3 Particle Size

			<u>Size (Microns)</u>
5	S Bioglass		90 - 355
	S Bioglass		500 - 710
	S Bioglass		90 - 710
10	F Bioglass		90 - 355
	F Bioglass		500 - 710
	F Bioglass		90 - 710

After a minimum of five weeks of the oral hygiene phase, the monkeys were taken to surgery.

15 Inhalation general anesthesia via nasal intubation was administered. Local anesthesia (2% Lidocaine with epinephrine 1:100,000) was infiltrated. Full thickness mucoperiosteal flaps were elevated and the area was debrided. The teeth were notched at the  
 20 level of the boney crest with a #1/4 round carbide bur in a slow speed handpiece. Osseous defects three to four millimeters deep were created with a high speed handpiece using a #2 or a #4 round carbide bur and copious water irrigation. Root planning was  
 25 accomplished with flame-shaped diamonds and finishing burs followed by hand instrumentation. Most sites prepared were two-walled interproximal defects, but tooth proximity and other anatomical considerations required the creation of three wall lingual or palatal  
 30 defects adjacent to some teeth. On lower second premolars (two-rooted teeth), lingual sites were prepared with removal of furcation bone simulating a deep class II furcation involvement.

Each animal had a total of eighteen sites available for implantation. Twelve sites received a bioactive glass implant. Four sites were implanted with Synthograft, Johnson & Johnson Dental Products, 5 East Windsor, New Jersey, Augmen, Miter Inc., Columbus, Ohio, Periograft or Alveolograft, Cook-Waite Laboratories, Inc., New York, New York. Two sites per animal served as controls.

10 The materials were mixed with saline in a disposable dish and packed into the defect. Flaps were replaced with 4:0 chromic sutures and the animals were placed on a softened diet for two weeks.

15 Starting the day of the surgery and for six days thereafter the animals were administered daily (IM) injections of Achromycin [Lee Sepe, W.W., Bowers, G.M., Laurence, J.J., Friedlaender, G.E., and Koch, R.W.: Clinical evaluation of freeze-dried bone allografts in periodontal osseous defects. Part II. J. Periodontol 49:9, 1979] (Tetracycline HCl) (20 20 mg/kg.)

The animals were sacrificed by overdose of sodium pentobarbital on the following time schedule: one animal at one month, two animals at four months and three animals at six months. The jaws were 25 removed and placed in 10% formalin. After fixation, they were decalcified and subdivided into small blocks each containing an experimental site. The tissues were embedded in paraffin, sectioned at approximately 6 microns and stained with hematoxylin and eosin.

30 When the various powders were implanted in the monkey model during the study the procedure was essentially the same as described above in the in-vitro experiment. Prior to placement, the materials were wet with one or two drops of sterile 35 water to essentially wet an area that was to be used.

The materials were carried from the dish with an orban knife or equivalent flat type instrument and carried to the periodontal site which was prepared to be approximately 3 mm deep. Most of these sites were 5 bleeding because they were surgically created sites.

The glass powders were easily transported to the site, and had the ability to pack very densely into the defects. On clinical evaluation it was found that the material seemed to have a hemostatic property 10 in that it was able to completely fill the defect and appeared to stop the bleeding. The glass powders mixed well with blood and formed a cohesive mix, which stopped the bleeding either due to intrinsic hemostatic properties or due to an efficient filling 15 of the defect such that it provided a physical barrier to bleeding.

The densely packed glass powders within the periodontal defects appeared translucent and with sufficient packing density that it appeared as if the 20 bone had never been removed.

It was found that this quality existed for all three of the particle size ranges of glass powders regardless of whether it was the S or the F fluoride formulation. The 500 to 710  $\mu\text{m}$  powders were the 25 least effective of the three. The 90 to 710  $\mu\text{m}$  powders were the most effective particle size range. The 90 to 355  $\mu\text{m}$  powders were in between the two in manipulation and packing properties. These clinical results in Patus monkeys were equivalent to the 30 in-vitro findings described above. The glass powders were compared in the in vivo monkey model, with tricalcium phosphate (Synthograft) which had a small particle size range of 250 to 500  $\mu\text{m}$ , and Augmen, which is a porous tricalcium phosphate, (TCP) in the 35 700 to 1000  $\mu\text{m}$  particle size range. When implanting

these materials into sites, there was difficulty in manipulating the material. When they were wet in the same way as glass, with sterile water, the materials were not cohesive, and were difficult to carry to the 5 sites. They fell off of the instruments and dissipated. When placed in a site that was bleeding, the TCP materials seemed to float or not stay in the defect and, with bleeding, washed out. There was a great difference between these TCP materials and glass 10 material in that the glass was hemostatic and it seemed that tricalcium phosphate caused increased bleeding.

The hydroxylapatite (HA) powders tested were Periograft which is equivalent in size (250-500  $\mu\text{m}$ ) 15 to Synthagraft (TCP). Alveolgraf (HA) and Augmen (TCP) are ridge augmentation materials of a larger particle size (700 to 1000  $\mu\text{m}$ ). These HA materials handled slightly better, Table 1, than tricalcium phosphates although they still could not be manipulated properly. 20 They tended to fall off of the instrument and when placed in a bleeding surgically created defect tended to float out. Their packability in the periodontal defect was markedly inferior to glass powders of all size ranges. These materials had even poorer 25 manipulation properties when implanted in a living model than in the in-vitro test.

Another superior clinical property noted for glass compositioning was when implanted into a site it was clearly visible in the site. When suction was 30 placed adjacent to the glass after implantation, it remained inside the defect and was resistant to surgical suction. This was not the case with either the TCP or HA calcium phosphate powders; suction could remove all these implant material from the defect very 35 quickly. Histological examination of the periodontal

defects after one month showed that with the optimum (90-710  $\mu\text{m}$ ) range of particle sizes of glass powders the following:

1. The material was retained in the implant area.
- 5 2. Adhesion of collagen to the large particles with no inflammation.
- 10 3. The transverse collagen fibers of the gingival which by insertion into the dentin of the tooth, prevent epithelial migration downward, are continuous with the collagen adherent to the larger glass particles.
- 15 4. The larger glass particles at the base of the implant site in contact with repairing bone become bonded to and surrounded by the new bone.
- 15 5. Superficial gingivitis does not extend into the implanted area filled with 90-710  $\mu\text{m}$  glass particles.
- 20 6. There is no epithelial migration into the implanted area.
- 25 7. The smallest glass particles were removed by macrophages and giant cells leaving space gradually infiltrated by adherent collagen and/or bone.
- 25 The consequences of the above 7 observations is that the periodontal defect becomes filled by large particles of glass with adherent collagen fibers and newly formed bone. Another consequence is that the transseptal fibers are continuous between neighboring teeth and large glass particles thereby preventing epithelial downgrowth into the defect.
- 30 35 Thus, the compositions of the invention are partially biodegradable in that smaller size particles are replaced ultimately by an ingrowth of tissue which serves to further lock the implant in place. The

larger particles function to form a bond with the surrounding tissue.

These above cited seven observations and the overall beneficial histological and physiological consequences of using the 90-710 $\mu\text{m}$  glass powders in a periodontal defect are an unexpected contrast to the behavior of TCP powders presently in use. The TCP powders provoke a strong inflammatory and giant cell reaction regardless of particle size, i.e., even the large 500-700 $\mu\text{m}$  TCP particles are being actively removed from the defect without restoration of the transseptal fibers and without prevention of epithelial migration. These observations of the presently used TCP materials are indicative of an unsatisfactory repair of the periodontal defect which are consistent with long term clinical findings for the TCP materials, even though they are still on the market.

In order to understand the unexpected differences in in-vitro and in-vivo behavior of glass powders compared with HA and TCP powders, physical characterization studies were undertaken. These studies showed that there are unexpected substantial physical differences between the synthetic hydroxyapatite and tricalcium phosphate materials as compared with the glass powders.

Table 4 is a compilation of results from nitrogen absorption isotherm analysis of the various powders tested in the in-vitro and the in-vivo experiments. The BET surface areas are listed in the first column, the total pore volume is in the second and the average pore radius calculated from the nitrogen absorption isotherm is in the 3rd column. It is apparent from this data that the synthetic apatite (HA) and tricalcium phosphate (TCP) materials have

substantially more surface area per unit weight of material than the glass powders. The total pore volume varies for the materials in such a way that it does not show a consistent difference. However, the 5 average pore radius of the HA and TCP materials is substantially less than the average pore radius of the glass materials.

The very small average pore radius for the synthetic HA and TCP materials is due to microporosity 10 of the materials which gives rise to their low density and tendency to float from the site when impacted into the periodontal defect. In contrast, the average pore radius of the glass powders is largely controlled by the geometric packing of the 15 particles into a cohesive mass. The glass powders do not show the very small microporosity characteristic of the presently used materials and therefore there is no tendency for them to float in the presence of the blood of the periodontal defect.

Table 4

## BONE GRAFTING MATERIAL

SAMPLE	(BET) SA	TOTAL PORE VOLUME	AVERAGE PORE RADIUS
Alveograf	$1.49\text{m}^2/\text{g}$	$5.33 \times 10^{-3}$ cc/g	71.2 Å
Augmen	$1.16\text{m}^2/\text{g}$	$3.84 \times 10^{-3}$ cc/g	65.9 Å
Periograf	$1.10\text{m}^2/\text{g}$	$2.22 \times 10^{-3}$ cc/g	40.3 Å
Synthograft	$1.90\text{m}^2/\text{g}$	$4.92 \times 10^{-3}$ cc/g	51.8 Å
90-710 NF 4555	$0.52\text{m}^2/\text{g}$	$8.35 \times 10^{-3}$ cc/g	319 Å
90-710 4556-F	$0.054\text{m}^2/\text{g}$	$6.89 \times 10^{-4}$ cc/g	254 Å
500-710F 4555.4F	$0.024\text{m}^2/\text{g}$	$5.23 \times 10^{-4}$ cc/g	431 Å
90-355NF 4555	$0.101\text{m}^2/\text{g}$	$7.84 \times 10^{-4}$ cc/g	155 Å
500-710 NF 4555-F	$0.092\text{m}^2/\text{g}$	$7.14 \times 10^{-3}$ cc/g	1546 Å
90-355 4555-F	$0.941\text{m}^2/\text{g}$	$1.16 \times 10^{-2}$ cc/g	247 Å

Note: All samples outgassed 20 hrs. @ 250° except  
(Alveograf = 44 hrs.) and (90-355, 4555-F = 96 hrs.)

The geometric packing of the glass powders of the wide particle size range (70 to 910  $\mu\text{m}$ ) results in a morticing of the small particles within the interstices of the large particles. Even a dry arrangement of this broad size range of glass powders, such as shown in a scanning electron micrograph (Fig. 1) illustrates how the particles can fit together into a tightly packed array.

The instantaneous chemical reaction of the glass particles with water and/or blood gives rise to the formation of a surface silica rich gel layer within which hydroxyapatite microcrystallites can form. When the gel formation and apatite crystallites occur within the capillary space separating the particles a cohesive mass results. (Fig. 2) The cohesive mass remains attached together during the insertion of it into the periodontal defect and the tight mechanical packing is responsible for the stoppage of bleeding. This hemostatic effect observed for the glass periodontal pack is due to the mechanical or occlusion of the bleeding capillary bed.

Results showing that it is mechanical occlusion of the blood supply in the periodontal defect rather than an alteration of blood chemistry were obtained during measurements on whole blood clotting time for the variety of implant materials tested in the in-vitro and in-vivo experiments. Table 5 compares the results from this clotting experiment. It can be seen from this table that there is no significant difference between the control clotting time of 4.34 minutes and the glass S formulas of 90 to 710  $\mu\text{m}$  particle size and 500 to 710 particle size. Each of those sizes results in 4.3 minutes of clotting time. The F formula glass powders do decrease

clotting time to values that are akin to the synthetic Periograft and Synthograft and Augmen materials. However, the HA and TCP materials are not hemostatic in the periodontal defect whereas both the 5 glass S formula and glass F formulas are. Consequently it can be concluded from these results that the interfacial surface chemistry of the glass is not responsible for the superb clotting behavior in the periodontal defect. Instead it must be mechanical 10 occlusion due to tight cohesiveness of the glass particles in their optimum size and their rapid interfacial surface reactions that form a cementing of particles by the gel and apatite interfacial phases as soon as they are in contact with water and/or blood.

15

Table 5

WHOLE BLOOD CLOTTING TIME		
	Control (0.35ml saline)	(time/minutes)
20		4.34
	Periograf	3.30
	Synthograft	4.00
	Bioglass S (500-710)	4.30
25	Bioglass S (90-710)	4.30
	Bioglass F (90-355)	3.30
	Bioglass F (500-710)	4.00
	Bioglass F (90-710)	3.40
	Augmen	3.00
30		

Bioactive and biocompatible glasses of the following weight percentage compositions may also be employed in the practice of the invention:

0206726

- 21 -

	<u>Component</u>	<u>Weight Percentage</u>
5	SiO <sub>2</sub>	45
	CaO	24.5
	Na <sub>2</sub> O	24.5
	P <sub>2</sub> O <sub>5</sub>	6.0
10	<u>Component</u>	<u>Weight Percentage</u>
15	SiO <sub>2</sub>	45
	CaO	12.25
	Na <sub>2</sub> O	24.5
	CaF <sub>2</sub>	12.25
	P <sub>2</sub> O <sub>5</sub>	6.0
20	<u>Component</u>	<u>Weight Percentage</u>
25	SiO <sub>2</sub>	40
	CaO	24.5
	Na <sub>2</sub> O	24.5
	B <sub>2</sub> O <sub>3</sub>	6.0
4)	<u>Component</u>	<u>Weight Percentage</u>
25	SiO <sub>2</sub>	52
	CaO	21.0
	Na <sub>2</sub> O	21.0
	P <sub>2</sub> O <sub>5</sub>	6.0

CLAIMS

1. A composition suitable for the repair of periodontal osseous defects comprising particulate bioactive and biocompatible glass, said particulate glass having a particle size in the range of from 5 about 90 to about 710 $\mu\text{m}$  and the following weight percentage composition:

	<u>Component</u>	<u>Weight Percentage</u>
	SiO <sub>2</sub>	40-52
	CaO	10-50
10	Na <sub>2</sub> O	10-35
	P <sub>2</sub> O <sub>5</sub>	2-8
	CaF <sub>2</sub>	0-25
	B <sub>2</sub> O <sub>3</sub>	0-10

2. The composition of Claim 1 wherein said 15 particulate glass has a particle size in the range of from about 90 to about 355 $\mu\text{m}$ .

3. The composition of Claim 1 wherein said particulate glass has a particle size in the range of from about 355 to about 500 $\mu\text{m}$ .

20 4. The composition of Claim 1 wherein said particulate glass has a particle size in the range of from about 500 to about 710 $\mu\text{m}$ .

5. The composition of Claim 1 comprising a mixture of (1) said particulate glass having a particle size 25 in the range of from about 90 to about 355 $\mu\text{m}$ , (2) said particulate glass having a particle size in the range of from about 355 to about 500 $\mu\text{m}$ , and (3) said

particulate glass having a particle size in the range of from about 500 to about 710 $\mu$ m.

6. The composition of Claim 5 comprising equal weights by thirds of each of said particulate glasses 5 1), 2) and 3).

7. The composition of Claim 1 additionally containing a liquid in admixture with said particulate glass in an amount sufficient to wet the particles of said glass.

10 8. The composition of Claim 7 wherein said liquid is aqueous.

9. The composition of Claim 8 wherein the amount of said blood in said mixture is from about 1/3 to about equal volume of said particulate glass.



(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 86304643.9

(51) Int. Cl.<sup>3</sup>: A 61 L 27/00  
A 61 K 6/06

(22) Date of filing: 16.06.86

(30) Priority: 19.06.85 US 746342

(71) Applicant: UNIVERSITY OF FLORIDA  
207 Tigert Hall  
Gainesville Florida 32611(US)

(43) Date of publication of application:  
30.12.86 Bulletin 86/52

(72) Inventor: Low, Samuel Bernard  
2435 N.W. 35th Terrace  
Gainesville Florida 32601(US)

(88) Date of deferred publication of search report: 13.01.88

(72) Inventor: Fetner, Alan Edward  
6508 N.W. 53rd Terrace  
Gainesville Florida 32606(US)

(84) Designated Contracting States:  
AT BE CH DE FR GB IT LI LU NL SE

(72) Inventor: Clark, Arthur Edward, Jr.  
2901 N.W. 41st Avenue  
Gainesville Florida 32605(US)

(72) Inventor: Hench, Larry Leroy  
1415 N.W. 94th Street  
Gainesville Florida 32606(US)

(72) Inventor: Wilson-Hench, June  
1415 N.W. 94th Street  
Gainesville Florida 32606(US)

(74) Representative: Hedley, Nicholas James Matthew et al,  
T.Z. Gold & Company 9 Staple Inn  
London WC1V 7QH(GB)

(54) Periodontal osseous defect repair.

(57) The present invention provides a composition for repair of periodontal osseous defects based on particulate bioactive and biocompatible glass. The particulate glass has a particle size in the range of 90 to 710  $\mu\text{m}$ , preferably it is a mixture of (1) glass having a particle size of 90 to 355  $\mu\text{m}$  (2) glass having a particle size of 355 to 500  $\mu\text{m}$ , and (3) glass having a particle size of 500 to 710  $\mu\text{m}$ . The glass composition is as follows:

Component	Weight Percentage
$\text{SiO}_2$	40-52
$\text{CaO}$	10-50
$\text{Na}_2\text{O}$	10-35
$\text{P}_2\text{O}_5$	2-8
$\text{CaF}_2$	0-25
$\text{B}_2\text{O}_3$	0-10



EP 86 30 4643

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	NL-A-8 304 129 (K. DE GROOT) * Page 1, line 28; page 1, lines 5-7; page 2, lines 5-21 *	1,2,7, 8	A 61 L 27/00 A 61 K 6/06
Y	---	1-3,7, 8	
Y	CERAMIC SOCIETY OF JAPAN, INTERNATIONAL CONGRESS ON GLASS, Kyoto, 8th-12th December 1974, pages 9-30 - 9-41, Ceramic Society, Kyoto, JP; L.L. HENCH: "Biomedical applications and glass corrosion" * Page 9-32, table I *		
Y	---	1-3	
A	US-A-4 131 597 (W. BLÜETHGEN) * Column 2, lines 29-45 *		TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	---		A 61 L
A	US-A-4 234 972 (L.L. HENCH)		A 61 K
A	---		
A	FR-A-2 230 598 (E. LEITZ)		
	-----		
The present search report has been drawn up for all claims			
Place of search	Date of compilation of the search	Examiner	
THE HAGUE	19-10-1987	PELTRE CHR.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			

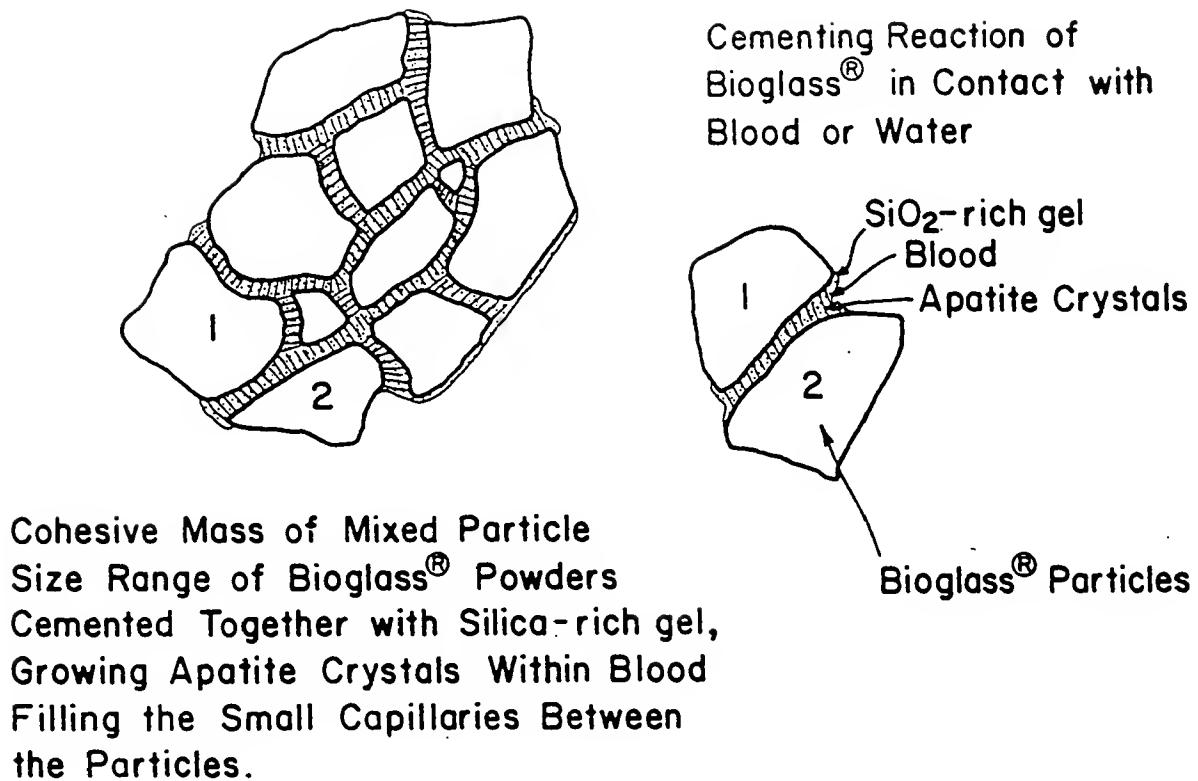


FIG. 2

0206726

FIG. I



SCANNING ELECTRON MICROGRAPH OF  
70 - 910  $\mu$ m BIOGLASS PARTICLES

1000  $\mu$ m